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Action of extracellular divalent cations on native α-amino-3-hydroxy- 5-methylisoxazole-4-propionate (AMPA) receptors

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Abstract

The effects of divalent cations on Ca2+-impermeable containing (GluR2 subunit) MPA receptors of hippocampal pyramidal neurones isolated from rat brain was studied using patch-clamping. Ca2+, Mg2+, Mn2+, Co2+, Ni2+ and Zn2+ inhibited currents induced by kainate and glutamate. Inhibition was fast, reversible and voltage independent. The rank order of activities was Ni2+ > Zn2+ > Co2+ > Ca2+ > Mn2+ > Mg2+. Cyclothiazide (0.1 mM) significantly reduced inhibition by divalent cations and 6, 7 dinitroquinoxaline-2.3-dione (DNQX). However, high concentrations of Ni2+ and DNQX inhibited AMPA receptors even in the presence of cyclothiazide. The inhibitory effect of divalent cations as well as DNQX was counteracted by an increase in agonist concentration. In the presence of divalent cations the EC50 values of kainate and glutamate were increased, but the maximal response was not changed. An increase in agonist concentration induced a parallel shift in the concentration-inhibition curve for a divalent cation. These data suggest a competitive-like type of inhibition. However, an increase in agonist concentration reduced the inhibitory action of Ni2+ less than that of DNQX. This gave evidence against direct competition between divalent cations and AMPA receptor agonists. A 'complex-competition' hypothesis was proposed to explain the inhibitory action of divalent cations; it is suggested that divalent cations form ion-agonist complexes, which compete with free agonist for agonist-binding sites on AMPA receptors. © 2005 The Authors Journal Compilation © 2005 International Society for Neurochemistry.

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Keywords

AMPA receptor, Chelation, Competition, Inhibition